

### Abstract of the Disclosure

The present invention relates to methods of mixing large numbers of heterologous genes, which are located on artificial chromosomes. The methods of the present invention are useful for evolution of cells and whole genomes to acquire new functionality(ies), such as the ability to synthesise novel secondary metabolites and/or the evolution of novel metabolic pathways. In particular the methods may involve mating or fusing two populations of cells, each population comprising different combinations of heterologous genes. Subsequently, desirable cells may be selected. In embodiments of the invention the heterologous genes are comprised within expression cassettes. The expression cassette can be in the form of a concatemer, and can be cut out using a restriction enzyme in order to make new combinations of expression cassettes.